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Original Research Article

Clinical evaluation of calcium dobesilate in diabetic retinopathy patients

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Abstract

Background: Diabetic Retinopathy (DR) is a common complication of diabetes, characterized by retinal microvascular changes that can lead to vision loss. Calcium dobesilate, a vascular-regulating medication, may help manage DR by reducing inflammation and capillary permeability.
Aim: This study aimed to evaluate the effects of oral calcium dobesilate on pro-inflammatory markers in patients with diabetic retinopathy.
Materials and Methods: A prospective interventional study was conducted from February 2023 to March 2024 at Netaji Subash Chandra Bose Subharti Medical College, Meerut. Fifty patients with type 2 diabetes were divided into three groups: Group A (17 patients with DR treated with calcium dobesilate), Group B (17 patients with DR receiving a placebo), and Group C (16 diabetic patients without retinopathy). Serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) were measured at baseline and after 12 weeks of treatment.
Results: After 12 weeks, Group A showed a significant reduction in IL-6 (from 4.82 pg/ml to 3.88 pg/ml, p = 0.039) and TNF-α levels (from 27.73 pg/ml to 24.01 pg/ml, p = 0.038), compared to Group B, which had no significant changes. CRP levels decreased in Group A (from 3.15 mg/L to 2.61 mg/L) but increased slightly in Group B.
Conclusion: Calcium dobesilate effectively reduces pro-inflammatory markers in diabetic retinopathy patients, suggesting its potential as a therapeutic option. Further studies are needed to confirm these findings and assess long-term outcomes.

Keywords: Diabetic retinopathy, Calcium dobesilate, Inflammatory markers, IL-6, TNF-α, CRP.

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1. Introduction

Diabetes Mellitus is one of the largest global health problem. Its burden is high and increasing globally as well as in developing countries such as India. This is primarily due to the increasing prevalence of overweight/obesity and unhealthy lifestyles. A study in 2019 showed that 77 million people were living with diabetes in India; this number is expected to rise to over 134 million by 2045. Type 2 diabetes, which constitutes the majority of patients, can cause many problems in the body. It affects both microvessels and macrovessels throughout the body. These problems are a major cause of morbidity and mortality in people with diabetes.[1]

Diabetic retinopathy (DR) is the most common microangiopathy in the diabetic population that leads to neovascularization, retinal edema, visual impairment and blindness. Diabetic retinopathy is one of the main causes of preventable acquired blindness in working-age adults in developed countries and is prevalent in 75 to 95 percent of diabetic patients after 15 years of disease onset.[2] The exact pathogenesis of diabetic retinopathy is not clear. Factors such as poor glycemic control, duration of diabetes and associated hypertension play a significant role in the development of diabetic retinopathy.[3] Diabetic macular edema is the common cause of vision loss in people with diabetic retinopathy.[4]

There are seven mechanisms by which calcium dobesilate treats diabetic retinopathy. (i) reducing retinal albumin leakage and capillary permeability, which protects the blood-retinal barrier (BRB)[5] (ii) inhibiting platelet

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aggregation and blood viscosity[6] (iii) up-regulating endothelium-dependent relaxation because of an increase in nitric oxide synthesis[7] (iv) inhibiting apoptosis of vascular endothelial cells in blood vessels[8] (v) antioxidant and antiradical activity[9] (vi) protecting against reactive oxygen species (vii) inhibiting the expression of the inflammatory and upstream VEGF regulator, ICAM-1.[10]

2. Aim and Objectives

1. To study the serum levels of pro-inflammatory markers (IL-6 and TNFα) and C-reactive protein in patients with diabetic retinopathy.
2. To study the effect of oral calcium dobesilate (500mg three times /day for 12 weeks) on serum levels of pro-inflammatory markers (IL-6 and TNFα) and C-reactive protein in patients with diabetic retinopathy.

3. Materials and Methods

The study was a prospective interventional study conducted at Netaji Subash Chandra Bose Subharti Medical College, Meerut, from February 2023 to March 2024. Informed consent was obtained from all 50 diabetic patients enrolled in the study who were subsequently divided into three groups:

Group A: Patients with diabetic retinopathy receiving oral Calcium dobesilate (500 mg three times a day).
Group B: Patients with diabetic retinopathy receiving a placebo.
Group C: Diabetic patients without retinopathy, serving as a control group.

Ethical clearance for the study was obtained from the institutional ethics committee prior to its initiation. Inclusion criteria included diabetic patients with retinopathy seeking treatment in this institute, while exclusion criteria involved a history of intraocular surgery, ocular trauma, inflammatory diseases, recent corticosteroid use, glaucoma, malignancies, and organ transplants. Clinical history, ocular examination, and blood tests were performed at baseline and after three months.

3.1. Clinical examination and measurements

1. Visual acuity and refractive status: Best corrected visual acuity was recorded at baseline and follow-ups.
2. Slit lamp biomicroscopy: Detailed examination of the anterior and posterior segments of the eye.
3. Fundus examination: Conducted using direct and indirect ophthalmoscopy to assess retinal changes.
4. Blood investigations: HbA1c levels and pro-inflammatory markers (IL-6, TNFα) were measured using ELISA kits.
5. Optical coherence tomography (OCT): Used to measure macular thickness.

3.2. Statistical analysis

Data was analyzed by using SYSTAT-13.2. 'The quantitative variables were evaluated using unpaired-T test and Anova test'. The quantitative variables were compared using the Chi-square test. 'For assessing the impact of variables odds ratio was calculated. A p-value of <0.05 was assumed statistically significant. Complete history of the patients was taken followed by a thorough general physical examination and ophthalmological examination.

4. Results

Table 1: Gender distribution among the study groups

Group	Female		Male		Total
	N	%	N	%	
Group A	6	35.3	11	64.7	17
Group B	12	70.6	5	29.4	17
Group C	7	43.8	9	56.3	16

The present prospective study was conducted in Netaji Subash Chandra Bose Subharti Medical College, Meerut during February 2023 to June 2024 among 50 diabetes mellitus patients. Out of 50 patients; 34 were having diabetic retinopathy (which included 17 patients of Diabetic retinopathy with type 2 Diabetes mellitus on calcium dobesilate 500mg thrice a day for 12 weeks (Group A) and 17 patients with Type II Diabetic mellitus who were given placebo (Group B) and 16 were not having diabetic retinopathy (Group C). The aim of the study was to evaluate the effect of oral calcium dobesilate (500mg three times /day for 12 weeks) on serum levels of pro-inflammatory markers (IL-6 and TNF α) and C-reactive protein in patients with diabetic retinopathy.

In all the groups; males were comparatively more as compared to females. (**Table 1**).

Table 2: Distribution of mean age among the study groups

Group	Mean Age (in years)	SD	Minimum	Maximum
Group A	52.882	9.137	38	71
Group B	56.471	9.139	37	71
Group C	50.688	12.371	33	71

Mean age was 52.88, 56.47 and 50.69 years in Group A (Diabetic Retinopathy with oral CaD), Group B (Diabetic Retinopathy with placebo), and Group C (Diabetes Mellitus without retinopathy) respectively.

Table 3: IL-6 comparison among the study groups

Group	**IL-6(pg/ml)**				**p-value**
	1st Day		**3rd Month**		
	Mean	**SD**	**Mean**	**SD**	
Group A	4.817	3.33	3.88	2.81	0.039*
Group B	3.011	1.32	3.05	1.31	0.86
Group C	2.968	1.36	2.74	1.45	0.72
p value					
Group A vs Group B	0.036*		0.043*		
Group A vs Group C	0.014*		0.18		
Group B vs Group C	0.81		0.61		

*: statistically significant

Table 4: IL-6 at first day and 3rd month according to grades of diabetic retinopathy

DR	**Il-6(pg/ml)**				**p value**
	1st Day		3rd Month		
	Mean	SD	Mean	SD	
No	2.97	1.36	2.74	1.45	0.19
Mild NPDR	3.68	2.88	3.39	2.43	0.07
Moderate NPDR	4.01	2.84	3.45	2.36	0.043*
Severe NPDR	4.19	2.21	3.62	1.74	0.038*

*: statistically significant

Table 5: TNF- α comparison among the study groups

Group	TNF- α(pg/ml)				**p value**
	1st Day		**3rd Month**		
	Mean	**SD**	**Mean**	**SD**	
Group A	27.73	23.83	24.01	21.96	0.38
Group B	41.86	28.45	42.35	29.07	0.85
Group C	16.19	14.16	15.47	12.79	0.77
p value					
Group A vs Group B	0.031*		0.009*		
Group A vs Group C	0.001*		0.001*		
Group B vs Group C	0.001*		0.001*		

*: statistically significant

Table 6: TNF- α at first day and 3rd month according to grades of diabetic retinopathy

DR	**TNF-** α(pg/ml)				**p-value**
	1st Day		**3rd Month**		
	Mean	**SD**	**Mean**	**SD**	
No	16.19	14.16	15.48	12.79	0.71
Mild NPDR	40.98	24.17	39.94	25.39	0.78
Moderate NPDR	31.63	31.92	30.09	30.88	0.73
Severe NPDR	28.72	23.84	25.95	24.06	0.57

At baseline mean IL-6 level was maximum in Group A (Diabetic Retinopathy with oral CaD) followed by Group B (Diabetic Retinopathy with placebo) and Group C (Diabetes Mellitus without retinopathy) respectively. After administering oral Calcium Dobesilate 500mg 3 times per day for 3 months mean IL-6 level was significantly decreased in Group A (Diabetic Retinopathy with oral CaD) as compared in Group B (Diabetic Retinopathy with placebo) and Group C (Diabetes Mellitus without retinopathy).

After 3 months of oral administration of Calcium Dobesilate (500mg 3 times a day for 3 months); mean IL-6 level in GROUP A (Diabetic Retinopathy with oral CaD) was significantly decreased in severe NPDR subjects (From 4.19

to 3.62) followed by moderate NPDR (from 4.01 to 3.45) as p<0.05 as compared to patients in Group B (Diabetic Retinopathy with placebo) and Group C (Diabetes Mellitus without retinopathy).

At baseline, mean TNF- α level was maximum in Group B (Diabetic Retinopathy with placebo) followed by Group A (Diabetic Retinopathy with oral CaD) and Group C (Diabetes Mellitus without retinopathy) respectively. After 3 months of administration of oral Calcium Dobesilate (500mg 3 times a day for 3 months); the mean TNF- α level was decreased in Group A (27.73 to 24.01) while it increased in Group B (from 41.86 to 42.35). When the mean TNF- α level was compared between Group A and Group B using t-test; a significant difference was reported as p<0.05.

After administering oral Calcium Dobesilate (500mg 3 times a day for 3 months); mean TNF- α level in Group A (Diabetic Retinopathy with oral CaD) was decreased maximum in severe NPDR subjects (from 28.72 to 25.95) followed by moderate NPDR subjects (from 31.63 to 30.09) as compared to Group B (Diabetic Retinopathy with placebo) and Group C (Diabetes Mellitus without retinopathy).

Table 7: CRP comparison among the study groups

Group	**CRP(mg/L)**				**p value**
	1st Day		**3rd Month**		
	Mean	**SD**	**Mean**	**SD**	
Group A	3.15	3.52	2.61	3.03	0.32
Group B	3.57	2.88	3.62	2.91	0.91
Group C	4.11	2.99	3.91	2.98	0.74
p-value					
Group A vs Group B	0.31		0.03*		
Group A vs Group C	0.042*		0.012*		
Group B vs Group C	0.14		0.55		

*: statistically significant

At baseline; the mean CRP level was maximum in Group C (Diabetes Mellitus without retinopathy) (4.11) followed by Group B (Diabetic Retinopathy with placebo) (3.57) and Group A (Diabetic Retinopathy with oral CaD) (3.15) respectively. After administration of oral calcium dobesilate 500mg 3 times per day for 3 months; the mean CRP level was decreased in Group A (Diabetic Retinopathy with oral CaD) while it increased in Group B (Diabetic Retinopathy with placebo). When the mean CRP level was compared Group A (Diabetic Retinopathy with oral CaD) and Group B (Diabetic Retinopathy with placebo using t-test; significant difference was reported as p<0.05.

Table 8: CRP at first day and 3rd month according to grades of diabetic retinopathy

DR	**CRP(mg/L)**				**p value**
	1st Day		**3rd Month**		
	Mean	**SD**	**Mean**	**SD**	
No	4.11	2.98	3.91	2.98	0.68
Mild NPDR	4.17	3.84	3.83	3.35	0.54
Moderate NPDR	2.77	2.46	2.64	2.57	0.79
Severe NPDR	2.81	2.88	2.53	2.92	0.63

After administering oral Calcium Dobesilate (500mg 3 times per day for 3 months); the mean CRP level in Group A (Diabetic Retinopathy with oral CaD) was decreased maximum in severe NPDR subjects (from 2.81 to 2.53) followed by moderate NPDR subjects (2.77 to 2.64) as compared to Group B (Diabetic Retinopathy with placebo) and Group C (Diabetes Mellitus without retinopathy).

5. Discussion

Diabetic retinopathy (DR) is a common complication of diabetes characterized by retinal microvascular changes, hemorrhages, edema, and neovascularization, which can lead to blindness.[11] Calcium dobesilate, a vascular-regulating medication, has been shown to reduce capillary permeability and inhibit sorbitol generation, thereby improving microcirculation and reducing the risk of retinal complications associated with diabetes.[12] However, its effectiveness in preventing the long-term progression of DR remains limited. This study aimed to evaluate the effects of oral calcium dobesilate (500 mg three times daily for 12 weeks) on serum levels of pro-inflammatory markers (IL-6, TNF-α) and C-reactive protein (CRP) in patients with DR.

5.1. Gender and age distribution

In all study groups, males were more prevalent than females, consistent with findings by Larsson et al,[13] Sachdev and Sahni[14] and Haas et al.[15] The mean ages in Groups A (52.88 years), B (56.47 years), and C (50.69 years) were similar to those reported in previous studies, indicating a typical age range for patients with diabetic retinopathy and diabetes mellitus without retinopathy.(**Table 1** and **Table 2**)

5.2. Diabetic retinopathy progression

Mild, moderate, and severe non-proliferative diabetic retinopathy (NPDR) was observed in Groups A and B, with no significant change in the grading of retinopathy at the first and third-month follow-ups. This aligns with previous studies, such as those by Haas et al[15] which found no statistically significant influence of calcium dobesilate on DR progression. Early studies indicated that calcium dobesilate

improved blood flow and microcirculation, reduced blood hyperviscosity, and lowered intraocular pressure, but these studies had small sample sizes. A larger, double-blind, placebo-controlled study showed that calcium dobesilate positively affected early DR progression by preventing blood-retina barrier disruption, independent of diabetes control.[16-19]

5.3. Inflammatory markers

At baseline, IL-6 levels were highest in Group A, followed by Groups B and C. After three months of calcium dobesilate administration, IL-6 levels significantly decreased in Group A, with minimal changes in Groups B and C (**Table 3** and **Table 4**). TNF-α levels were highest in Group B at baseline and decreased significantly in Group A after treatment, while they increased in Group B (**Table 5** and **Table 6**). CRP levels were highest in Group C at baseline but decreased in Group A after treatment (**Table 7** and **Table 8**). These findings indicate a significant anti-inflammatory effect of calcium dobesilate, consistent with previous studies by Hernandez-Da Mota et al which also reported higher serum cytokine levels in patients with diabetic retinopathy.[20]

5.4. HbA1c levels

At baseline, HbA1c levels were comparable among the groups. After three months, HbA1c levels decreased in Group A (with calcium dobesilate) and increased in Group B (placebo). The reduction in HbA1c levels in Group A suggests that calcium dobesilate may help improve glycemic control. This finding aligns with Noura M. Almutairi et al[21] who highlighted the significance of HbA1c as a risk factor for diabetic retinopathy progression.

5.5. Central macular thickness (CMT)

Baseline CMT levels were similar across all groups. After three months of calcium dobesilate administration, CMT remained stable in Groups A and C but increased in Group B. Although calcium dobesilate has been studied extensively as a vasculo-protective agent for DR, its effectiveness in reducing macular edema has been inconsistent. Some studies showed no significant effect of calcium dobesilate on clinically significant diabetic macular edema (CSME) in type 2 diabetes mellitus, while others reported beneficial effects on microaneurysms, retinal hemorrhages, exudates, and blood viscosity.[22]

6. Limitations

Although this study achieved some important findings, some limitations need to be considered i.e.

1. First, the sample size was relatively small, which may affect the broad applicability of the results. Due to the limited sample size, there is need to interpret the results with caution and be wary of overgeneralization.
2. Additionally, this study was conducted at a single medical center, which may result in regional and population-specific factors affecting the results. To increase the external validity of the study results, multicenter study designs could be considered in the future.
3. The time span of the study was relatively short and long-term follow-up and study may help to more comprehensively assess treatment effects and long-term patient prognosis.
4. The study did not also fully consider the impact of other medical conditions, medications or lifestyle factors that patients may have on the results.

7. Conclusion

Calcium dobesilate demonstrates good efficacy in the treatment of diabetic retinopathy. It effectively inhibited the levels of IL-6, TNF-α and CRP that contribute to improved outcomes for patients with Diabetic Retinopathy. Large-scale studies are needed to validate these findings and delve deeply into treatment mechanisms and long-term effects.

8. Source of Funding

None.

9. Conflict of Interest

None.

10. Ethical Approval

Ethical No.: SMC/UECM/2023/511/257.

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